REMARKS

Claims 11, 12, 16, 22-27, 32-34, 44, 50-54, 56, 58-69, 73-81 and 83-109 are pending and under examination.

Rejections Under 35 USC § 102

The rejection of claims 11, 16, 24-27, 32, 34, 44, 50-54, 56, 58-61, 67, 68, 75-79, 81, 83-86, 88, 89, 91, 92, 94, 95, 97, 98 and 100-109 under 35 USC § 102(b), as being anticipated by Turner et al., Breast Cancer Res. Treatment 46:69 (1997) as evidenced by Krajewski et al., Endocrine-Related Cancer 6:29-40 (1999), and the Breastcancer.org website entitled "Stages of Breast Cancer" (www.breastcancer.org/symptoms/diagnosis/staging.jsp) submitted as Exhibit 2 in the response filed July 23, 2008, is respectfully traversed. The Office Action states on page 4 that Krajewski and Exhibit 2 are provided to explain the information present in the Turner reference and do not expand the meaning of the term "invasive carcinoma" used by Turner et al. Additionally, the Office asserts that the invasive breast cancer studied by Turner et al. was stages I and II, irrespective of the reliance on Krajewski and Exhibit 2. Applicant respectfully disagrees with both of the Office's assertions. Applicant respectfully maintains, for the reasons of record, that Turner et al. does not anticipate the claimed methods and further provides the following remarks.

First, to clarify the record, contrary to the Office's assertion on page 4, lines 16-18 of the Office Action, Applicant did not present arguments of teaching away with respect to the anticipation rejection in the Response filed May 11, 2010. Applicant did present arguments of teaching away in response to the obviousness rejections, which is a proper argument to rebut an alleged *prima facie* case of obviousness.

Second, as previously argued on the record, the Office's use of the disclosure of Krajewski et al. and Exhibit 2 to support the anticipation rejection is improper (*In re Baxter Travenol Labs.*, 952 F.2d 388, 21 USPQ2d 1281 (Fed. Cir. 1991) and *Scripps Clinic & Research Foundation V. Genetech, Inc.*, 927 F.2d 1565, 18 USPQ2d 1001 (Fed. Cir. 1991)). Applicant respectfully submits that the use of Krajewski et al. in combination with Exhibit 2 is expanding the meaning of the term "invasive carcinoma" used by Turner et al. Contrary to the Office's

assertion, the evidence of record shows that one skilled in the art would have understood that invasive carcinoma, as taught by Turner, could include stage I, II, III, or IV breast cancers or any of the thirteen TNM stage groupings. Specifically, Applicants directs the Office to Exhibit 1 (a printout from the Breastcancer.org website entitled "Non-Invasive or Invasive Breast Cancer?" (www.breastcancer.org/symptoms/diagnosis/invasive.jsp)), Exhibit 2, *supra*, and Exhibit 3 (Markman, Basic Cancer Medicine pgs. 35-37 (1997)) submitted with the response filed July 23, 2008. Exhibit 1 defines invasive (or infiltrating) breast cancers to be cancers that have started to break through normal breast tissue barriers and invade surrounding area. Exhibit 2 explicitly discloses that breast cancer at stage I, stage II, stage III or stage IV is considered to be invasive. Additionally, according to the tumor-node-metastasis (TNM) staging system described in Exhibit 3, there are thirteen distinguishable TNM stage groupings within stage I to stage IV of breast cancer (see page 36 of Exhibit 3).

Third, Applicant respectfully disagrees with the Office's assertion that the invasive breast cancer studied by Turner et al. was stages I and II, irrespective of the reliance on Krajewski and Exhibit 2. Turner et al. do not disclose, in any context, that the invasive carcinoma of the breast studied by Turner et al. was stages I and II. Turner et al. do not even mention the terms "stage I" or "stage II" or any art recognized equivalent. On the contrary, Turner et al. are completely silent as to whether the invasive carcinoma samples were stage I, II, III or IV or any of the thirteen TNM stage groupings known in the art (see discussion above). Additionally, the Office's own admission on page 10, lines 16-17 of the Office Action issued November 24, 2009 states "Turner et al. do not expressly disclose that the invasive carcinoma of breast cancer include state I and/or stage II cancer." (emphasis added). In contrast to the disclosure of Turner et al., the claimed methods are directed to prognostic and screening methods for individuals having breast cancer, wherein the individual has stage I breast cancer in which the cancer is infiltrating but has no lymph node involvement or the individual has stage II breast cancer in which the cancer is infiltrating but has spread no further than the lymph nodes local to breast. Accordingly, Turner et al. do not teach, expressly or inherently, the claimed methods relating to stage I or stage II of breast cancer, as claimed. Absent such teachings, Applicant respectfully submits that Turner et al. cannot anticipate the claims. Accordingly, Applicant respectfully requests that this rejection be withdrawn.

Rejections Under 35 USC § 103

The rejection of claims 11, 12, 16, 24-27, 32-34, 44, 50-54, 56, 58-61, 67-69, 75-81, 83-86, 88, 89, 91, 92, 94, 95, 97, 98 and 100-109 under 35 U.S.C. §103(a) as allegedly obvious over Turner et al., *supra* in view of Sano et al. (US Patent 5,665,539), as evidenced by Krajewski et al., *supra*, and Exhibit 2, *supra*, is respectfully traversed. The Office Action states on page 5 that Applicant presented the same arguments as for the 102(b) rejection and these arguments are not persuasive for the reasons set forth in the 102(b) rejection. Applicant respectfully submits that the arguments previously presented against the 102(b) rejection were not the same as the arguments presented against the above obviousness rejection. Applicant herein reiterates the same arguments previously presented to rebut the obviousness rejection over Turner et al. in view of Sano et al., as evidenced by Krajewski et al. and Exhibit 2 and presents additional arguments for the Office's consideration. Applicant respectfully submits that the disclosures of Turner et al., alone or in combination with Sano et al. as evidenced by Krajewski et al. and Exhibit 2, do not teach or suggest the claimed prognostic or screening methods relating to stage I or stage II of breast cancer and the level of cytosolic BAG-1 protein expression.

The Office Action issued November 24, 2009 states on page 4 that the invasive carcinoma (IC) studied by Turner et al. is early stage, as evidenced by the disclosure of Krajewski et al. The Office Action then states that early stage invasive cancer of breast includes stages I and II breast cancer, as evidenced by Exhibit 2. Furthermore, the Office Action states that stage I breast cancer is defined as invasive breast cancer (cancer cells are breaking through to or invading neighboring normal tissue) in which the tumor measures up to two centimeters and no lymph nodes are involved, and stage II breast cancer is defined as invasive breast cancer in which the tumor measures at least two centimeters but not more than five centimeters, or cancer has spread to the lymph nodes under the arm on the same side as the breast cancer. Thus, Turner et al. allegedly studied BAG-1 expression in breast cancer which is infiltrating [invasive] but has spread no further than the lymph nodes local to breast. Applicant respectfully disagrees for the following reasons.

At best, Turner et al. disclose, using a retrospective study, that the 10-year overall survival (OS) and distant disease free survival (DDFS) for patients with overexpression of

cytoplasmic BAG-1 in invasive carcinoma (IC) specimens was 75% and 70%, respectively, as compared with 62% and 35% for tumors with low cytoplasmic BAG-1 levels ($p = 0.06$). Applicant maintains that a skilled artisan working in the cancer field would have understood that this relatively small differential in overall survival rate between specimen over- or under-expressing BAG-1 with p=0.06 is not significant enough to conclusively suggest that BAG-1 can be a reliable diagnostic tool for predicting survival, let alone being a diagnostic tool for predicting survival of patients with stage I or stage II of breast cancer as claimed. Applicant previously provided Exhibit A (Zar, Biostatistical Analysis, Prentice-Hall, Inc., Chapter 6, pgs. 79-86, (1999)) provided with the Response filed May 11, 2010. Zar discloses on pages 81-82:

> As explained below, a probability of 5% [$p = 0.05$] or less is commonly used as the criterion for rejection of H_0 [the null hypothesis]. The probability used as the criterion for rejection is called the *significance level*,* denoted by α (the lowercase Greek letter, alpha). [*see page 81, last paragraph, emphasis added*]
>
> By experience, and hence by convention, an α of 0.05 is usually considered to be a "small enough" chance of committing a Type I error [a rejection of a null hypothesis when it is in fact true], while not being so small as to result in "too large a chance" of a Type II error [not rejecting the null hypothesis when it is in fact false]. But there is nothing sacrosanct about the 0.05 level. Although it is the most widely used significance level, researchers may decide for themselves whether it is more important to minimize one type of error or the other [*see page 82, last paragraph, emphasis added*]

In other words, by Turner et al. identifying a p value of 0.06, one skilled in the art would most likely conclude that there was no statistically significant correlation between OS and DDFS for invasive carcinoma patients with overexpression of cytoplasmic BAG-1. Additionally, the evidence provided by Exhibit A corroborates Dr. Reed's statement that the patient survival difference of cytosolic staining of BAG-1 cited in Turner et al. for invasive carcinoma (IC) was not statistically significant (p = 0.06) (see Reed Declaration submitted previously as Exhibit 2 with the Response filed December 13, 2006). Applicant further submits that, although p value is not a direct factor for determining obviousness, a reasonable expectation of success is a factor to be considered by the Office in determining obviousness (MPEP §2143.02) and a p value that indicates there was no statistically significant correlation, as disclosed by Turner et al., would most likely have negatively affected one of skill in the art's expectation of success in practicing a

prognostic or screening method, as claimed. Contrary to the disclosure of Turner et al, it is the Applicant, in the present invention, that discovered 1) a statistically significant correlation between 10-year OS and DMFS (distant metastasis-free survival) for patients with overexpression of BAG-1 protein in stages I and II of breast cancer that was 90% and 84%, respectively, as compared with 40% and 40% for those with low BAG-1 levels ($p<0.001$) (see page 35 of the application as filed, lines 5-14, and Figure 1); and 2) patients whose tumors contained high levels of cytosolic BAG-1 protein are more likely to enjoy long-term survival and freedom from tumor recurrence or spread and distant metastases, compared to those with tumors containing low levels of cytosolic BAG-1 (see page 35 of the application as filed, line 31 to page 36, line 3). Thus, one skilled in the art would not have had a reasonable expectation of success in practicing the claimed methods.

Furthermore, the disclosure of Turner et al. as evidenced by Krajewski et al., actually teaches away from the claimed methods. At best, Krajewski et al. disclose higher levels of BAG-1 nuclear immunostaining (>20%) correlated with longer OS among patients with early stage breast cancer ($p<0.001$) (see page 36, first column, lines 19-23). This is in contrast to the claimed prognostic or screening methods, wherein the level of cytosolic BAG-1 protein expression is determined relative to a reference level of BAG-1. Thus, in view of the disclosure of Turner et al. that there was no statistically significant correlation between OS and DDFS for invasive carcinoma patients with overexpression of cytoplasmic BAG-1, and the disclosure of Krajewski et al. that higher levels of BAG-1 nuclear immunostaining correlated with OS among patients with early stage breast cancer, one skilled in the art would not have had a reasonable expectation of success in practicing the claimed methods.

Accordingly, Turner et al. as evidenced by Krajewski et al. and Exhibit 2 neither teaches nor suggests the claimed prognostic methods relating to stage I or stage II of breast cancer and the level of cytosolic BAG-1 protein expression. The disclosure of Sano et al. does not cure these defects either, as it contains no teaching or suggestions that would complement the disclosure of Turner et al. as evidenced by Krajewski et al. and Exhibit 2 to arrive at the claimed methods. Therefore, Applicant respectfully maintains that the claimed methods are unobvious over Turner et al., alone or in combination with Sano et al. as evidenced by Krajewski et al. and Exhibit 2. Accordingly, Applicant respectfully requests that this rejection be withdrawn.

The rejection of claims 11, 16, 24-27, 32, 34, 44, 50-54, 56, 58-68, 75-79, 81, and 83-109 under 35 U.S.C. § 103(a) as allegedly obvious over Turner et al., *supra*, in view of Sauter et al., Br. J. Cancer 76:494-501 (1997) as evidenced by Krajewski et al., *supra*, and Exhibit 2, *supra*, is respectfully traversed. The Office Action states on page 5 that Applicant presented the same arguments as for the 102(b) rejection and these arguments are not persuasive for the reasons set forth in the 102(b) rejection.

Applicant respectfully maintains, for the reasons of record and as articulated herein, that the claimed methods are unobvious over Turner et al., alone or in combination, with Sauter et al. As discussed in the above obviousness argument, Turner et al. as evidenced by Krajewski et al. and Exhibit 2 neither teaches nor suggests the claimed prognostic methods relating to stage I or stage II of breast cancer and the level of cytosolic BAG-1 protein expression. The disclosure of Sauter et al. does not cure these defects either, as it contains no teaching or suggestions that would complement the teaching of Turner et al. as evidenced by Krajewski et al. and Exhibit 2 to arrive at the claimed methods. Therefore, Applicant respectfully maintains that the claimed methods are unobvious over Turner et al., alone or in combination with Sauter et al. as evidenced by Krajewski et al. and Exhibit 2. Accordingly, Applicant respectfully requests that this rejection be withdrawn.

The rejection of claims 11, 16, 24-27, 32, 34, 44, 50-54, 56, 58-68, 75-79, 81, and 83-109 under 35 U.S.C. § 103(a) as allegedly obvious over Turner et al., *supra*, in view of Love (U.S. Patent No. 6,221,622) as evidenced by Krajewski et al., *supra*, and Exhibit 2, *supra*, is respectfully traversed. The Office Action states on page 6 that Applicant presented the same arguments as for the 102(b) rejection and these arguments are not persuasive for the reasons set forth in the 102(b) rejection.

Applicant respectfully maintains, for the reasons of record and as articulated herein, that the claimed methods are unobvious over Turner et al., alone or in combination with Sauter et al. As discussed in the above obviousness argument, Turner et al. as evidenced by Krajewski et al. and Exhibit 2 neither teaches nor suggests the claimed prognostic methods relating to stage I or stage II of breast cancer and the level of cytosolic BAG-1 protein expression. The disclosure of Love does not cure these defects either, as it contains no teaching or suggestions that would

complement the teaching of Turner et al. as evidenced by Krajewski et al. and Exhibit 2 to arrive at the claimed methods. Therefore, Applicant respectfully maintains that the claimed methods are unobvious over Turner et al., alone or in combination with Love as evidenced by Krajewski et al. and Exhibit 2. Accordingly, Applicant respectfully requests that this rejection be withdrawn.

The rejection of claims 11, 16, 22-27, 32, 34, 44, 50-54, 56, 58-61, 67, 68, 73-79, 81, 83-86, 88, 89, 91, 92, 94, 95, 97, 98, and 100-109 under 35 U.S.C. § 103(a) as allegedly obvious over Turner et al., *supra*, in view of Mather et al., Clin. Cancer Res., 4:1857-1856 (1998) and McGuire et al. (US Patent 6,188,964) as evidenced by Krajewski et al., *supra*, and Exhibit 2, *supra*, is respectfully traversed. The Office Action states on page 6 that Applicant presented the same arguments as for the 102(b) rejection and these arguments are not persuasive for the reasons set forth in the 102(b) rejection.

Applicant respectfully maintains, for the reasons of record and as articulated herein, that the claimed methods are unobvious over Turner et al., alone or in combination, with Mather et al. and McGuire et al. As discussed in the above obviousness argument, Turner et al. as evidenced by Krajewski et al. and Exhibit 2 neither teaches nor suggests the claimed prognostic methods relating to stage I or stage II of breast cancer and the level of cytosolic BAG-1 protein expression. The disclosures of Mather et al. and/or McGuire et al. do not cure these defects, as they contains no teaching or suggestions that would complement the teaching of Turner et al. as evidenced by Krajewski et al. and Exhibit 2 to arrive at the claimed methods. Therefore, Applicant respectfully maintains that the claimed methods are unobvious over Turner et al., alone or in combination with Mather et al. and/or McGuire et al. as evidenced by Krajewski et al. and Exhibit 2. Accordingly, Applicant respectfully requests that this rejection be withdrawn.

The rejection of claims 11, 12, 16, 22-27, 32-34, 44, 50-54, 56, 58-69, 73-81, and 83-109 under 35 U.S.C. § 103(a) as allegedly obvious over Turner et al., *supra*, in view of Mather et al., *supra*, McGuire et al., *supra*, Sano et al., *supra*, and Love, *supra*, is respectfully traversed. The Office asserts that one of skill in the art would have had a reasonable expectation of success because Turner et al. had shown that the 10-year overall survival (OS) and distant disease free survival (DDFS) for breast cancer patients with overexpression of BAG-1 in IC specimens was

75% and 70%, respectively, compared to 62% and 35% for tumors with low cytoplasmic BAG-1 levels. The Office also asserts Applicant's arguments of *p* value are not persuasive because *p* value is allegedly not a factor for determining obviousness. Applicant respectfully maintains that the claimed methods are unobvious over Turner et al., alone or in combination, with Mather et al. and/or McGuire et al. and/or Sano et al. and/or Love.

As discussed above, at best, Turner et al. analyzed invasive carcinoma patient samples for a correlation of OS and DDFS with overexpression of cytoplasmic BAG-1, which revealed a *p* value of 0.06. This would most likely indicate to one skilled in the art that there was no statistically significant correlation between OS and DDFS for invasive carcinoma patients with overexpression of cytoplasmic BAG-1 (see arguments above with respect to Exhibit A). Exhibit A corroborates Dr. Reed's statement that the patient survival difference of cytosolic staining of BAG-1 cited in Turner et al. for invasive carcinoma (IC) was not statistically significant ($p = 0.06$) (see Reed Declaration submitted previously as Exhibit 2 with the response filed December 13, 2006). Applicant further submits that, although *p* value is not a direct factor for determining obviousness, a reasonable expectation of success is a factor to be considered by the Office in determining obviousness (MPEP §2143.02) and a *p* value that indicates there was no statistically significant correlation, as disclosed by Turner et al., would most likely have negatively affected one of skill in the art's expectation of success in practicing a prognostic or screening method, as claimed. Contrary to the disclosure of Turner et al., it is the Applicant, in the present invention, that discovered 1) a statistically significant correlation between 10-year OS and DMFS (distant metastasis-free survival) for patients with overexpression of BAG-1 protein in stages I and II of breast cancer that was 90% and 84%, respectively, as compared with 40% and 40% for those with low BAG-1 levels ($p<0.001$) (see page 35 of the application as filed, lines 5-14, and Figure 1); and 2) patients whose tumors contained high levels of cytosolic BAG-1 protein are more likely to enjoy long-term survival and freedom from tumor recurrence or spread and distant metastases, compared to those with tumors containing low levels of cytosolic BAG-1 (see page 35 of the application as filed, line 31 to page 36, line 3). Thus, one skilled in the art would not have had a reasonable expectation of success in practicing the claimed methods.

Furthermore, the invasive carcinoma specimens as taught by Turner et al. would likely be considered by one skilled in the art to include stage I, stage II, stage III, or stage IV breast

cancers. This is supported by the evidence of record, specifically Exhibit 1, *supra*, Exhibit 2, *supra*, and Exhibit 3, *supra*, submitted with the Response filed July 23, 2008. Exhibit 1 defines invasive (or infiltrating) breast cancers to be cancers that have started to break through normal breast tissue barriers and invade surrounding area. Exhibit 2 explicitly discloses that breast cancer at stage I, stage II, stage III or stage IV is considered to be invasive. Additionally, according to the tumor-node-metastasis (TNM) staging system described in Exhibit 3, there are thirteen distinguishable TNM stage groupings within stage I to stage IV of breast cancer (see page 36 of Exhibit 3). Thus, Applicant submits that one skilled in the art would understand that invasive carcinoma, as taught by Turner et al., could include stage I, II, III, or IV breast cancers or any of the thirteen TNM stage groupings. Applicant also submits that, based on the description in Turner et al. and what was well known in the art, one skilled in the art would not know which stage of breast cancer the IC samples of Turner et al. belong and certainly would not know if the samples were from stage I or stage II breast cancer patients. Thus, because Turner et al. does not teach or suggest that the samples were from stage I or stage II breast cancer patients, one skilled in the art would not have had a reasonable expectation of success in practicing the claimed methods, which are directed to prognostic and screening methods for individuals having breast cancer, wherein the individual has stage I breast cancer in which the cancer is infiltrating but has no lymph node involvement or the individual has stage II breast cancer in which the cancer is infiltrating but has spread no further than the lymph nodes local to breast.

Accordingly, Turner et al. neither teaches nor suggests the claimed prognostic methods relating to stage I or stage II of breast cancer and the level of cytosolic BAG-1 protein expression. The disclosures of Mather et al. and/or McGuire et al. and/or Sano et al. and/or Love do not cure these defects, as they contain no teaching or suggestions that would complement the teaching of Turner et al to arrive at the claimed methods. Therefore, Applicant respectfully maintains that the claimed methods are unobvious over Turner et al., alone or in combination with Mather et al. and/or McGuire et al. and/or Sano et al. and/or Love. Accordingly, Applicant respectfully requests that this rejection be withdrawn.

CONCLUSION

In light of the remarks herein, Applicants submit that the claims are now in condition for allowance and respectfully request a notice to this effect. The Examiner is invited to call the undersigned agent if there are any questions.

To the extent necessary, a petition for an extension of time under 37 C.F.R. 1.136 is hereby made. Please charge any shortage in fees due in connection with the filing of this paper, including extension of time fees, to Deposit Account 502624 and please credit any excess fees to such deposit account.

Respectfully submitted,

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